REMARKS

Claims 21-23 and 27-37 are pending in the application, with Claims 27-37 being withdrawn from consideration pursuant to restriction requirement. Claims 21-23 stand rejected. Claim 22 is hereby canceled. Claims 21 and 23 are hereby amended, with support for said amendments being found generally throughout the specification and specifically within Claim 22 and pages 2 and 15-17 of the specification (see for instance "Activity assay and inhibition of PDE activity" on page 16). Claims 21 and 23, as amended, thus now stand pending.

Claim Rejections

1. 35 USC § 112, second paragraph

Claims 21-23 stand rejected under 35 USC 112, second paragraph, as being indefinite, specifically for lack of antecedent basis in the preamble of Claim 21.

Applicants have amended Claim 21 to address the antecedent basis in the preamble. Applicants therefore respectfully submit that Claims 21 and 23, as herein amended, are now proper and respectfully submit that the 112, second paragraph rejection be withdrawn.

2. 35 USC § 103(a)

A) Claims 21-23 stand rejected under 35 USC 103(a) as being unpatentable over Frenette (WO 00/64874). The Examiner alleges Frenette teaches (pg 2) the existence of multiple PDE4's raises the prospect of obtaining inhibitors that are selective for individual isoforms of PDE4. Frenette is also alleged to disclose treatment of a laundry list of 25 or so diseases with compounds that are selective and potent inhibitors of PDE4. The last two diseases to which the compounds of Frenette "may be put include" arterial sclerosis/atherosclerosis (pg 11). The Examiner acknowledges that Frenette does not teach screening and identifying modulators of PDE4D, but that same would be

obvious in light of Frenette's alleged teaching of obtaining inhibitors with regard to PDE4. Applicants respectfully traverse and overcome said rejection.

First, and contrary to the Examiner's assertion, Frenette at best discloses inhibitors of PDE4 enzymes, but does not disclose activity of the PDE4 enzymes themselves with the development of any diseases, much less atherosclerosis or stenosis. Frenette does not disclose, teach or otherwise suggest step 1 of Claim 21 (measuring activity of a PDE4 target), nor does Frenette disclose, teach or otherwise step 2 of Claim 21 (administering a compound suspected to be an activator or inhibitor of PDE4 to the PDE4 target). Therefore at least two steps of Applicants claimed invention are not disclosed, taught or even suggested by Frenette. One of ordinary skill in the art arguably would not have even considered Frenette, given that Frenette seemingly does not contain any data showing a connection between PDE4 activity and the development of restenosis or atherosclerosis, respectively.

Second, there is no enablement anywhere in Frenette supporting the alleged laundry list of uses to which the Frenette compounds "may be put" in lines 14-22 on page 11. Applicants submit that Frenette at best only enables inflammation of the lung. There are no examples nor data nor experimentation which support the Frenette compounds being used for restenosis or atherosclerosis. Absent enablement, Applicants submit that Frenette et al would not be considered by one of ordinary skill of the art as teaching or suggesting or motivating one of ordinary skill in the art with regard to the method of Applicants' Claim 1. Absent enablement, Applicants respectfully submit that Frenette is not proper 103(a) art.

The lack of teaching, suggestion or motivation in Frenette for atherosclerosis or restenosis is clear to one of ordinary skill in the art. Frenette et al (WO 00/64874) relates to heterosubstituted pyridines derivatives that are inhibitors of PDE4 at concentrations at which they have little or no inhibitory action on other PDE isoenzymes. These compounds inhibit the human recombinant PDE4 enzyme and also elevate

cAMP in isolated leukocytes. The compounds thus prevent, alleviate or reduce inflammation in the lungs, such as that induced by carrageenan, platelet-activating factor (PAF), interleukin-5 or antigen challenge. The compounds also suppress the hyperresponsiveness of airway smooth muscle seen in inflamed lungs (WO 00/064874, p. 2, lines 25 - 32). According to p. 3, first paragraph the compounds are of use in medicine, especially in the prophylaxis and treatment of asthma.

Thus, the focus of WO 00/64874 is on compounds having anti-inflammatory activities. This is further underlined by the assays for determining the biological activity of the inventive compounds (see p. 38 - 40). Assay 1:"LPS and FMLP induced TNF alpha and LTB4 assay in human whole blood" is an assay for testing the anti-inflammatory activity of compounds. The second assay "Anti-allergic activity in vivo" tests the effect of the compounds on an IgE mediated allergic pulmonary inflammation induced by inhalation of antigen by sensitized guinea pigs. Therefore, at best, the only determined activities of the inventive compounds would allegedly be their anti-inflammatory and anti-allergic activity.

WO 00/64874 at best discloses compounds having anti-inflammatory and/or anti-allergic activity. It does not disclose a compound having anti-atherosclerotic activity. It does not support or disclose any data for anti-atherosclerotic activity. A mere listing of possible diseases that might be treatable by the inventive compounds without support of in vitro data is not an enabling teaching for a person skilled in the art. WO does not enable the laundry list of possible diseases in line 14-22 on page 11, much less enable a treatment of atherosclerosis.

Applicants therefore respectfully submit that Frenette lacks support for treating arterial restenosis and atherosclerosis as Frenette lacks any in vitro or in vivo biological activity data showing that the inventive compounds could be used for the treatment of arterial restenosis and atherosclerosis. In other words, Frenette is not enabling with

respect to the use of the inventive compounds for the treatment of arterial restenosis and atherosclerosis.

Therefore, Applicants respectfully submit that WO 00/64874 lacks an enabling teaching with regard to PDE4 inhibitors for the treatment of arterial restenosis and atherosclerosis.

In conclusion, Applicants respectfully submit that Frenette does not teach, disclose nor suggest at least two steps of Applicants' claimed invention and that accordingly Claims 21 and 23, as amended, are novel and non-obvious. Furthermore Applicants submit that Frenette is not an enabling disclosure with regard to PDE4 inhibitors for the treatment of arterial restenosis and atherosclerosis. Applicants therefore respectfully request that the 103(a) rejection be withdrawn and that said claims be put into condition for allowance.

B) Claims 21-23 are also rejected under 35 USC 103(a) as being unpatentable over Gretarsdottir (US 2005/0287551 A1) The Examiner alleges Gretarsdottir teaches (para 6, pg 1) 9 isoforms of PDE4D and the PDE4D gene is involved in the pathogenesis of stroke. The Examiner acknowledges that the reference fails to teach inhibiting restenosis, but that it would be obvious to apply an atherosclerosis compound to restenosis. Applicants respectfully traverse and overcome said rejection.

Applicants's response of November 29, 2007 respectfully noted that the Gretarsdottir (US 2005/0287551 A1) reference relied upon by the Examiner is a continuation-in-part application. With regard to the alleged teaching originally cited by the Examiner in paragraphs 6-8 and 11 of Gretarsdottir, Applicants therein respectfully submitted that this "teaching" seemingly first appears in the continuation-in-part application No. 10/419,723 filed on April 18, 2003. The priority date of the present application (April 10, 2003) predates the cited CIP date of Gretarsdottir and as such

Gretarsdottir is not proper prior art against Applicant's claimed invention. Accordingly, Applicants respectfully requested that the 103(a) rejection be withdrawn.

The Examiner now contends that paragraphs 7, 13 and 17 of US 2004/0091865, filed September 25, 2002 teaches atherosclerosis. Applicants respectfully traverse and overcome this rejection.

As noted in above in Applicants response of November 29, 2007 with regard to paragraphs 6-8 and 11, Paragraphs 7, 13 and 17 of US 2004/0091865 also simply do not disclose anything that might be relevant for the claims of the present invention as to atherosclerosis. Paragraphs 7, 13 and 17 of the '865 application refer only to stroke. Atherosclerosis is not mentioned!. Restenosis is not mentioned! For purposes of clarity, Applicants herein cite for the record paragraphs 7, 13 and 17 of US 2004/0091865 in full:

Paragraph 7 of US 2004/0091865

> [0007] As described herein, it has been discovered that the gene that encodes phosphodiesterase 4D (hereinafter referred to as "PDE4D") has been correlated through human linkage studies to stroke, particularly ischemic strokes and transient ischemic attacks. Five new exons, herein referred to as 4D7-1, 4D7-2, 4D7-3, 4D6 and 4D8 have been identified. Three novel splice variants have also been identified (see FIG. 4).

Paragraph 13 of US 2004/0091865

> [0013] The invention further relates to methods of diagnosing a predisposition to stroke. The methods of diagnosing a predisposition to stroke in an individual include detecting the presence of a polymorphism in PDE4D, as well as detecting alterations in expression of an PDE4D polypeptide, such as the presence of different splicing variants of PDE4D polypeptides. The alterations in expression can be quantitative, qualitative, or both quantitative and qualitative. The methods

of the invention allow the accurate diagnosis of stroke at or before disease onset, thus reducing or minimizing the debilitating effects of stroke.

Paragraph 17 of US 2004/0091865

[0017] Additionally, the invention pertains to pharmaceutical compositions comprising the nucleic acids of the invention, the polypeptides of the invention, and/or the agents that alter activity of PDE4D polypeptide. The invention further pertains to methods of treating stroke, by administering PDE4D therapeutic agents, such as nucleic acids of the invention, polypeptides of the invention, the agents that alter activity of PDE4D polypeptide, or compositions comprising the nucleic acids, polypeptides, and/or the agents that alter activity of PDE4D polypeptide. The invention further provides a method of diagnosing susceptibility to stroke in an individual. This method comprises screening for an at-risk haplotype in the phosphodiesterase 4D gene that is more frequently present in an individual susceptible to stroke, compared to the frequency of its presence in a healthy individual, wherein the presence of the at-risk haplotype is indicative of a susceptibility to stroke.

The cited paragraphs do not disclose atherosclerosis nor restenosis. Therefore, none of these cited paragraphs discloses, teaches or suggests a connection between PDE4 and atherosclerosis and restenosis. Accordingly, one of ordinary skill in the art would not find any teaching, suggestion or motivation to use PDE4 for identifying a compound which inhibits atherosclerosis or restenosis.

As the cited 2004/0091865 application does not teach, suggest or motivate one of ordinary skill in the art, Applicants respectfully submit that the 2004/0091865 application is not relevant 103(a) art against Applicants claim 21 as herein amended. Applicants therefore also respectfully submit that the priority date of the present application (April 10, 2003) predates the cited CIP date of Gretarsdottir 2005/028755 and as such Gretarsdottir is not proper prior art against Applicant's claimed invention.

Accordingly, Applicants respectfully request that the 103(a) rejection be withdrawn and that Claims 21 and 23, as herein amended, be put into condition for allowance.

No further fee is required in connection the filing of this Amendment. If any additional fees are deemed necessary, authorization is given to charge the amount of any such fee to Deposit Account No. 08-2525.

Respectfully submitted,

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